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(71) Applicant: OTSUKA PHARMACEUTICAL CO., LTD.
9, Kandatsukasacho 2-chome
Chiyoda-ku Tokyo 101(JP)

(72) Inventor: Oshiro, Yasuo
61, Yoshinohoncho-6-chome
Tokushima-shi(JP)

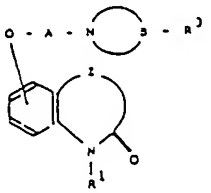
(72) Inventor: Osaki, Masaaki
864-26, Omatsu
Kawauchicho Tokushima-shi(JP)

(72) Inventor: Kikuchi, Tetsuro
157-13, Komatsunishi
Kawauchicho Tokushima-shi(JP)

(74) Representative: Lamb, John Baxter et al,
MARKS & CLERK 57/60 Lincoln's Inn Fields
London WC2A 3LS(GB)

(54) Preparation of pharmaceutical compositions for the treatment of hypoxia.

(57) In the preparation of a pharmaceutical compositions to the treatment of hypoxia there is used, as active ingredient, a compound of the formula:



(I)

in which R^1 is a hydrogen atom or a lower alkyl, lower alkenyl, lower alkynyl or phenyl-lower alkyl group.

Z is a group of the formula 

(in which R^2 is a hydrogen atom or a lower alkyl group; and the bond ⋯ is a single or double bond), a group $-(CH_2)_3-$, $-O-CH_2-$ or $-S-CH_2-$;

R^3 is a pyridyl group, or a phenyl group optionally substituted with up to three substituents selected from halogen atoms and lower alkyl, lower alkoxy and hydroxy groups;

the group

is a group or

and A is a lower alkylene group;

provided that when the group 

is a group 

then Z is a group of the formula 

and R^3 is neither a pyridyl group nor a phenyl group having a hydroxy group as the substituent; or provided that when R^3 is a pyridyl group, then Z is a group of the formula

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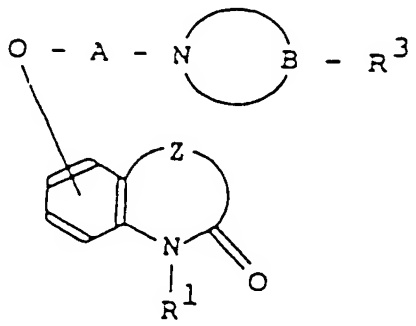
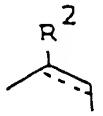
PREPARATION OF PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF HYPOXIA

The present invention relates to a method for the preparation of a pharmaceutical composition for the treatment of hypoxia using, as active ingredient, a compound of formula 1 below, or a salt thereof,



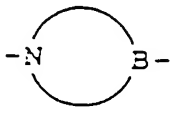
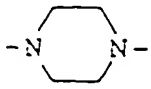
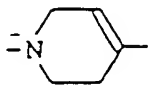
(1)

in which R^1 is a hydrogen atom or a lower alkyl, lower alkenyl, lower alkynyl group or phenyl-lower alkyl group.

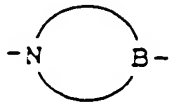
Z is a group 

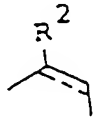
(in which R^2 is a hydrogen atom or a lower alkyl group, and the bond --- is a single or double bond), or a group $-(CH_2)_3-$, $-O-CH_2-$ or $-S-CH_2-$;

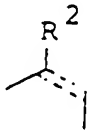
R^3 is a pyridyl group or a phenyl group optionally substituted with up to 3 substituents selected from halogen atoms and lower alkyl, lower alkoxy and hydroxy groups;

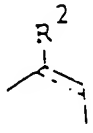
the group  is a group  or  ;

and A is a lower alkylene group;

provided that when the group  is a group  ,

then Z is a group 

and R^3 is neither a pyridyl group nor a phenyl group having a hydroxy group as substituent; or provided that when R^3 is a pyridyl group, Z is a group 

Compounds of formula (1) in which Z is a group 

already have been disclosed, see for example, Japanese Patent Application Kokai (Laid-Open) Nos. 54-160389 (1979) 55-2693 (1980), 55-124766 (1980), 55-129268

(1980), 56-49359 (1981), 56-49361 (1981), 56-164186 (1981), 57-145872 (1982) and others. Additionally, compounds of formula (1), in which Z is a group $-O-CH_2-$ or $-S-CH_2-$ have already been disclosed, see for example, Japanese Patent Application Kokai (Laid-Open) No. 59-70675 (1984) and others. Furthermore, compounds of formula (1) in which Z is $-(CH_2)_3-$ have been disclosed, for example in Japanese Patent Application Kokai (Laid-Open) No. 57-193461 (1982) and others.

However, the known compounds of general formula (1) have only been disclosed as having central nervous system controlling activities and anti-histaminic activities.

We have now found, in accordance with the present invention, that compounds of formula (1) possess activities for improving hypoxia, which activities could not have been anticipated from the central nervous system controlling activities and anti-histaminic activities previously disclosed.

Accordingly, one object of the present invention is to provide a method for the preparation of a pharmaceutical compound for the treatment of hypoxia characterized by using, as active ingredient, a compound of formula (1).

Another object of the present invention is to provide the use of a compound represented by the general formula (1) as an anti-oxidant.

Generally speaking, oxygen is an essential element for the living body for sustaining life by release of energy and by metabolism. Oxygen is converted into so-called "active oxygen radicals", for example oxygen anion radicals, peroxide ions, hydroxyl radicals, etc., in various biochemical reactions, such as energy releasing reactions, enzymatic reations and other reactions caused by exposure to ultraviolet rays and various radiations.

The active oxygen radicals are indeed usrful for the living body in the actions of oxygenase and of phagocytosis carried out by leucocytes. On the other hand, the active oxygen radicals promote the peroxidation of unsaturated fatty acids, such as oleic acid, linoleic acid, linolenic acid and arachidonic acid, etc., which unsaturated fatty acids are abundant in the living body and are the main constituents of the biomembranes. The peroxidation of such unsaturated fatty acids produces peroxidized substances such as peroxidized lipids. Furthermore, similarly to the abovementioned active oxygen radicals, said peroxidized substance also produce alkoxy radicals and hydroxyl

radicals which will attack the biomembranes and result in disorders of the biomembranes and deactivation of various useful enzymes working in the living body. [See, "TAISHA" (metabolisms), Vol. 15, No. 10, (1978), The Special Issue on Active Oxygen].

On the other hand, there are some other enzymes, such as superoxide dismutase (hereinafter referred to as "SOD"), catalase, glutathion peroxide, etc., in the living body. These enzymes prevent the deactivation of metabolisms from the attack caused by the active oxygen radicals. Additionally, there are several vitamins, such as tocopherols (vitamin E groups) having anti-oxidative activities in the living body.

Generally, the normal homeostasis mechanisms in the living body are sustained by the actions of these enzymes and vitamins having antioxidative activities. However, sometimes the prophylaxis mechanisms in the living body maintained by the action of these enzymes and vitamins may be adversely affected for certain reasons, and the formation of active oxygen radicals in an amount exceeding the ability of the prophylaxis mechanisms in the living body, as well as the formation and accumulation of peroxidized substances, are observed.

In such cases, when the prohylaxis mechanisms in the living body are defected, then several severe disorders

such as various diseases caused by the aggregation of platelets, inflammations, disorders of the liver, arteriosclerosis, hemolysis, senescence or presbyopherenia, retinosis, disorders of the lungs, disorders of the heart and the lungs caused by the actions of certain drugs, ischematic coronary heart disease and the like may occur accompanying the progressive chain reactions of the peroxidation.

Hitherto, compounds having activity for scavenging active oxygen radicals, which are considered to be the main factors of the above-mentioned various diseases, and for preventing or lowering the formation and accumulation of the peroxidized substances in the living body were known and generally referred to as antioxidants. A number of studies of prophylaxis and curative effects using these antioxidants have been reported.

Enzymatic preparations containing SOD and other enzymes as mentioned previously are reported in "SUPEROXIDE-TO-IGAKU" (Superoxide and Medicines) by Yoshihiko Ohyanagi, pages 137 to 141, published by Kyoritsu Publishing Co., Ltd.; "SAISHIN-NO-IGAKU" (Modern Medicine)-Special Issue of active Oxygen and Its Medicinal Roles, Vol. 39, NO. 7, (1984); "ENSHOH" (Inflammations), Vol. 1, page 699, (1981); Ibid., Vol.

2, page 367, (1982); Current Therp. Rep., Vol. 20, pages 62 to 69, (1976); "Perspective Inflammation", published by Red-Wood Burn Ltd., pages 527 to 544, (1977); Acta. Physiol. Scand., Vol. 49, No. 2, Suppl. pages 59 to 65, (1980); Proc. Nat. Acad. Sci., U.S.A., Vol. 79, pages 7509 to 7513, (1982); "Pathology of Oxygen" published by Academy Press, Inc., pages 85 to 97, (1982); J. Clinic. Invest., Vol. 67, page 983, (1981); Ibid., Vol. 70, pages 650 to 658, (1982); "Pathology of Oxygen" published by Academy Press, Inc., pages 261 to 275, (1982); Biochem. Biophys. Acta, Vol. 542, pages 28 to 38, (1978); Bull. European Physiopathol. Resp., Vol. 17, Suppl. pages 287 to 288, (1981); "Pathology of Oxygen" published by Academy Press, Inc., pages 277 to 302, (1982);, Reports on Studies of Behcet's Disease, issued from Specified Intractable Disease Research Group, Ministry of Public Health and Welfare, the Japanese Government (1982 - 1983); J. Immunol., Vol. 128, page 2770, (1982); articles of butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), - tocopherol (vitamin E) and others, reported by Makoto and Hidetaka Tanaka, "IYAKU-JOURNAL" (Pharmaceutical Journal), Vol, 19, No. 12, pages 2351 to 2359, (1983); by Toshihiko Suematsu, Ibid., Vol, 19, No. 5, pages 909 to 914, (1983); Arch. Biochem. Biophys., Vol., 227, pages 534 to 541, (1976); Adv. Cancer Res., Vol. 26, page 197, (1978) and others.

Compounds of formula (1) possess good activities for improving anoxemic and hypoxic symptoms and syndromes accompanied therewith. More particularly, compounds of formula (1) and their salts are useful as, for example, cerabral activators, curative and/or improving agents for cerebral blood vessel disturbance (such as cerebral hemorrhage, cerebral infraction, subarachnoidal hemorrhage, hypertensive encephalopathy, etc.), agents for improving disturbance of consciousness caused by encephalitis, cerebral tumours, head injuries, metabolism disturbances, chemical poisoning and physical injuries, curative and/or improving agents for prognostic symptoms caused by the above-mentioned diseases, curative and/or improving agents for depression of attention, hyperanakinesia, speech disturbance and mental retardation, curative agents for amnesia, curative agent for presbyophrenia, agent for respiratory arrest caused by poisoning with potassium cyanide, improving agent for hypoxia, preventive agent for arrhythmia caused by the shortage of oxygen and heart failure, and others.

Additionally, compounds of formula (1) and salts thereof possess activity for scavenging active oxygen radicals and for preventing or reducing the formation of peroxidized lipids in the living body. Therefore, compounds of formula (1) and salts thereof are useful as

prophylactic and treating agents for various disturbances and diseases caused by the excessive formation of the above-mentioned active oxygen radicals, the accumulation of peroxidized lipids in the living body or for deficiencies of protective mechanisms in the living body against such active oxygen radicals and peroxidized lipids. Thus, compounds of formula (1) and salts thereof are useful as anti-arteriosclerosis agents, anti-inflammatory agents, analgesics, treating agents for autoimmune diseases, inhibitory agents for aggregation of platelets, hypotensive agents, anti-hyperlipemia agents, prophylactic and treating agents for retinosis of immature infant and for cataract and the like.

Furthermore, compounds of formula (1) and salts thereof are useful as anti-oxidative agents for oils and fats contained in various processed food products.

When the group R^1 or the group R^2 in formula (1) is a lower alkyl group, it may suitably be a C_1-C_6 straight or branched chain alkyl group such as a methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl or hexyl group. When a lower alkenyl group, the group R^2 may be a C_2-C_6 straight or branched chain alkenyl group, such as a vinyl, allyl, 2-butenyl, 3-butenyl, 2-methylallyl, 2-pentenyl or 2-hexenyl group. When a

lower alkynyl group, R^1 may, for example, be a straight or branched-chain C_2-C_6 alkynyl, such an an ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl or, 2-hexynyl group. When R^1 is a phenyl-lower alkyl group it may be one in which the alkyl moiety is a straight or branched chain C_1-C_6 alkylene group, such as a benzyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1,1-dimethyl-2-phenylethyl, 5-phenylpentyl, 6-phenylhexyl or 2-methyl-3-phenylpropyl group. When R^1 is a halogen atom, it may be, for example, a fluorine, chlorine, bromine or iodine. When R^1 is a lower alkoxy groups it may be a straight or branched chain C_1-C_6 alkoxy group, such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy or hexyloxy group.

When R^3 is a phenyl group having 1 to 3 substituents selected from halogen atoms and lower alkyl, lower alkoxy group and hydroxyl groups, the halogen, lower alkyl and lower alkoxy substituents may as described above for R^1. Particular examples of groups R^3 are phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-iodophenyl, 4-iodophenyl, 3,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,4-difluoro-

phenyl, 3,5-dibromophenyl, 3,4,5-trichlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 3-isopropylphenyl, 4-hexylphenyl, 3,4-dimethylphenyl, 2,5-dimethylphenyl, 2,3-dimethylphenyl, 3,4,5-trimethylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 4-isopropoxyphenyl, 4-hexyloxyphenyl, 3,4,5-trimethoxyphenyl, 3-methyl-4-chlorophenyl, 2-chloro-6-methylphenyl, 2-methoxy-3-chlorophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl and 3,4-dihydroxyphenyl groups.

The lower alkylene group A may, for example, be a straight- or branched-chain C_1-C_2 alkylene group, such as a methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene or hexamethylene group.

Certain of the compounds of formula (1) are, in themselves, new compounds and are provided as a further features of the invention. These compounds are:

7-{4-(4-Methylphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril;

6-{3-[4-(3-Methylphenyl)-1-piperazinyl]-propoxy}-2H-1,4-benzoxazin-3(4H)-one;

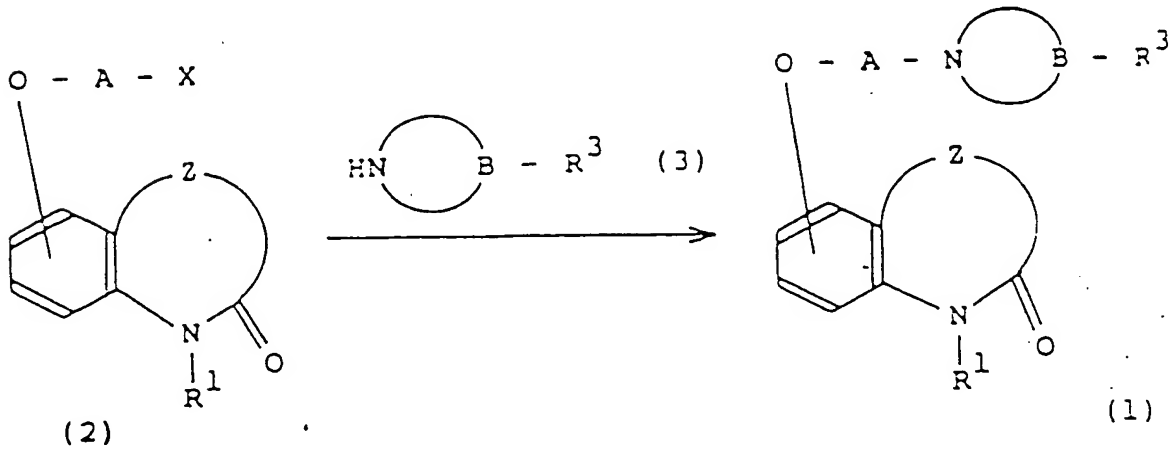
7-{3-[4-(3-Chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril;

7-{3-[4-(4-Chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril;

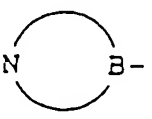
7-{3-[4-(3-Methylphenyl)-1,2-5,6-tetrahydro-1-pyridyl]propxy}-3,4-dihydrocarbostyril; and

6-{3-[4-(2,3-Dimethylphenyl)-1-piperazinyl]-propoxy}-2H-1,4-benzoxazin-3(4H)-one.

Compounds of formula (1) can be prepared by various methods, and a preferred method is that in accordance with the reaction scheme:



(2) (1)

(wherein R^1, R^3, A, Z and  B-

are the same as defined above; and X is a halogen atom, a lower alkanesulphonyloxy group, an arylsulphonyloxy group or an aralkylsulphonyloxy group). Thus compound (1) can be prepared by reacting a compound (2) with a compound (3).

Both compounds (2) and (3) to be used as starting materials are known compounds. When X is a lower alkanesulphonylox group it may for example be a methanesulfonyloxy, ethanesulphonyloxy, isopropane-sulphonyloxy, propanesulphonyloxy, butanesulphonyloxy, tert-butanesulphonyloxy, pentanesulphonyloxy or hexanesulphonyloxy group. When an arylsulphonyloxy group, X may be, for example, a substituted- or unsubstituted- or unsubstituted-aryl-sulphonyloxy group, such as phenylsulphonyloxy, 4-methyl-phenylsulphonyloxy, 2-methylsulphonyloxy, 4-nitrophenylsulphonyloxy, 4-methoxyphenylsulphonyloxy, 3-chlorophenylsulphonyloxy or α-naphthylsulphonyloxy groups. When X is an aralkylsulphonyloxy group it can be a substituted- or unsubstituted-aralkylsulphonyloxy group, such as a benzylsulphonylooxy, 2-phenylethylsulphonyloxy, 4-phenylbutylsulphonyloxy, 4-methylbenzylsulphonyloxy, 2-methylbenzylsulphonyloxy, 4-nitrobenzylsulphonyloxy, 4-methoxybenzylsulphonyloxy, 3-chlorobenzylsulphonyloxy or α-naphthylmethylsulphonyloxy group.

The reaction of the compound of formula (2) with the compound of formula (3) can be carried out in the absence, but generally in the presence of, an inert solvent, at room temperature to 200°C, preferably at 60 to 120°C, and the reaction is completed within about several hours to 24 hours. Suitable inert solvents include ethers such as dioxane, tetrahydrofuran, ethylene glycol, dimethyl ether, etc.; aromatic hydrocarbons such as benzene, toluene, xylene, etc; lower alcohols such as methanol, ethanol, isopropanol, etc.; and polar solvents such as dimethylformamide, dimethyl sulphoxide, acetone, acetonitrile, N-methylpyrrolidone, hexamethylphosphoric triamide.

The above reaciton is advantageously carried out using a basic compound as deacidifying agent. Suitable basic compounds are, for example, potassium carbonate, sodium carbonate, sodium hydroxide, sodium hydrogen carbonate, sodium amide, sodium hydride, 1,8-diazabicyclo[5,4,0]-7-undecene and tertiary amines such as triethylamine, tripropylamine, pyridine and quinoline.

The reaction can also be carried out if necessary with the addition of an alkali metal iodide, such as potassium iodide or sodium iodide.

The ratio of the compound of formula (2) to the compound of formual (3) is generally equimolar up to a molar excess quantity of the latter to the former; preferably an equimolar quantity upto 5 moles, more preferably, 1 to 1.2 moles of the compound of formula (3) to the compound of formula (2).

Thus obtained compounds of formula (1) can be separated and purified by usual separation techniques, for example solvent extraction, dilution, recrystallization, column chromatography, preparative thin-layer chromatography and the like.

The compounds of formula (1) used according to the invention include, of course, their stereo and optical isomers.

Compounds of formula (1) can easily be converted into their acid-addition salts by reaction with pharmaceutically acceptable acids, and the present invention also includes the use of such acid-addition salts. Examples of available pharmaceutically acceptable acids include inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, and hydrobromic acid, etc; and organic acids such as acetic acid, oxalic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, malonic acid, methanesulphonic acid, benzoic acid, etc.

The compounds of formula (1) can be used to make any of the usual forms of pharmaceutical compositions together with usual pharmaceutically acceptable carriers. The nature of pharmaceutically acceptable carriers will of course depend on the desired form of the pharmaceutical composition and thus there may be used diluents and excipients such as fillers, diluents, binders, wetting agents, disintegrating agents, surface active agents, lubricants, etc. There is no particular restriction as to the administration unit forms and the pharmaceutical compositions may be of any desired form including tablets, pills, powders, liquors, suspensions, emulsions, granules, capsules, suppositories, injection preparations (including solutions, suspensions, etc.) ointments, etc.

In order to make tablets, carriers which are widely used in this field can be used, for example, excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, crystalline cellulose, silicic acid, etc.; binding agents such as water, ethanol, propanol, simple sirup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shelac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.; disintegrating agents such as dried starch, sodium alginate, agar-agar powder, laminalia powder, sodium hydrogen carbonate,

calcium carbonate, esters of polyoxyethylene sorbitan fatty acids, sodium laurylsulphate, monoglyceride of stearic acid, starch lactose, etc.; disintegration inhibitors such as sucrose, stearin, coconut butter, hydrogenated vegetable oils, etc.; absorption accelerators such as quaternary ammonium bases, sodium laurylsulphonate, etc.; wetting agents such as glycerin, starch, etc.; adsorbing agents such as starch, lactose, kaolin, bentonite, colloidal silicic acid, etc.; and lubricants such as purified talc, stearic acid salts, boric acid powder, polyethylene glycols, etc. If necessary, the tablets can be further coated with coating materials to make them into coated tablets, for example tablets coated with sugar, tablets coated with gelatin film, tablets coated with enteric coating layers, tablets coated with films or double layer tablets as well as multiple layer tablets, etc.

To make pills, any carrier which is known and used widely in this field can be used, for example, excipients such as glucose, lactose, starch, coconut butter, hydrogenated vegetable oils, kaolin, talc, etc.; binders such as powdered gum arabic, powdered tragacanth gum, gelatin, ethanol, etc.; disintegrating agents such as laminaria, agar-agar, etc.

To make suppositories, carriers which are known and widely used in this field can also be used, for example, polyethylene glycols, coconut butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthesized glycerides, etc.

To make preparations for injection, solutions and suspensions are prepared and further sterilized and are preferably isotonic to blood. In preparing preparations for injection in the form of solutions, emulsions and suspensions, any carrier which is known and used in this field can also be used, for example water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, etc. In these instances, adequate amounts of sodium chloride, glucose or glycerin may be added to make the desired injection preparations isotonic. Furthermoremore concentrated dissolving agents, buffer solutions, analgesic agents may be added. Also colouring materials, preservatives, perfumes, seasoning agents, sweetening agents and other medicines may be added to the desired pharmaceutical preparations, if necessary.

To make the preparation in the form of a paste, cream or gels, diluents which are known and used in these fields can be also used, for example white

petrolatum, paraffin, glycerin, cellulose derivatives, polyethylene glycols, silicones, bentonite, etc.

The amount of compound of formula (1) or salt thereof present in the pharmaceutical composition is not specifically restricted, and can be selected from a wide range, and generally from 1 to 70% by weight of the compound or salt thereof may be present in the pharmaceutical composition.

Methods for administering the above-mentioned pharmaceutical composition are not specifically restricted, thus, the compositions can be administered in various forms of pharmaceutical preparations depend on the age, the distinction of sex, the degree of symptoms and other conditions of the patient without any restriction. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally; injection preparations are administered intraveneously singly, or administered with usual injectible transfusions such as

glucose solutions, amino acids solutions, etc.; if necessary, the injection preparations are administered singly intramuscularly, intracutaneously, subcutaneously or intraperitoneally; and the suppositories are administered into rectum.

The dosage of the above-mentioned pharmaceutical compositions can be selected suitably according to the methods for administrations, the age of the patiant, the distinction of sex and other conditions as well as the degree of the symptoms, and generally 0.2 to 200 mg/kg/day of compound represented by the general formula (1) or salt thereof may be used.

Reference Example 1

2.0 Grams of 7-(3-chloropropoxy)-3,4-dihydrocarbostyril and 1.6 g of sodium iodide were admixed with 60 ml of acetone, and the mixture thus obtained was stirred at 40 to 50°C for 2 hours. Then to this reaction mixture was added 60 ml of dimethylformamide, next acetone was removed by evaporation under reduced pressure, and 1.74 g of 4-(3-methylphenyl)-1,2,5,6-tetrahydropyridine and 2 ml of triethylamine were added thereto, further the whole mixture was stirred at 50 to 60°C for 6 hours. This reaction mixture was concentrated under reduced pressure, and to the residue thus obtained was added 80 ml of 5%-sodium hydrogen carbonate aqueous solution and stirred so as to crystallize the organic substance in the mixture. The precipitate was collected by filtration, washed with

water, and dried. Recrystallized from ethanol-water to yield 1.8 g of 7-{3-[4-(3-methylphenyl)-1,2,5,6-tetrahydro-1-pyridyl]-propoxy}-3,4-dihydrocarbostyril. Colorless flake-like crystals. Melting point: 143 - 145°C.

Reference Example 2

4.8 Grams of 7-(3-chloropropoxy)-3,4-dihydrocarbstyril and 3.5 g of sodium iodide were admixed with 50 ml of acetone, and the mixture thus obtained was refluxed for 3 hours. Then to this reaction mixture was added 40 ml of dimethylformamide, next acetone was removed by evaporation under reduced pressure, and 3.9 g of 4-(4-methylphenyl)-piperazine and 3.0 g of triethylamine were added thereto, further the whole mixture was stirred at 70 to 80°C for 7 hours. After removal of the solvent by evaporation under reduced pressure, 60 ml of 5%-sodium hydrogen carbonate aqueous solution was added to the resulting residue. Then this mixture was extracted with chloroform, and the chloroform layer was wahsed with water twice, dried then the solvent was removed by evaporation to obtain the residue. Recrystallized from ethanol to obtain 6.0 g of 7-{3-[4-(4-methylphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril. Yellow needle-like crystals. Melting point: 149 - 150°C.

By using suitable starting materials and by methods similar to that described in the above-mentioned Reference Example 2, there were prepared compounds as follows:

7-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propoxy}-

3,4-dihydrocarbostyril

Colorless needle-like crystals (recrystallized from ethanol. Melting point: 156 - 158°C.

7-{3-[4-(4-Chlorophenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril

Light yellow prism-like crystals (recrystallized from ethanol). Melting point: 200 - 202°C.

7-{3-[4-(3-Methoxyphenyl)-1-pieprazinyl]propoxy}-3,4-dihydrocarbostyril

Colorless needle-like crystals (recrystallized from ethanol). Melting point: 142 - 143°C.

Pharmacological Test (Survival test under hypoxic condition)

This test was conducted by procedures similar to those described in an article reported in "Arch. Int. Pharmacodyn., Vol. 233, page 137, (1978)".

ICR-strain male mice (weighing 20 to 30 g) were used as the test animals. Four mice were used as one test group, the mice were placed in a glass desciccator with which a stop valve was equipped. Inside pressure of the desciccator was reduced until 180 mm-Hg by sucking the air by using a vacuum pump, then the stop valve was closed.

Survival time of each of the test mice was determined as a length of time between the beginning of the vacuum pump operation and the arrest of breathing of the mouse.

Each of the test compounds was orally administered to the mouse at 15 minutes before the beginning of the

vacuum pump operation.

The survival time of the mouse of the reference group was referred to as 100, and the ratio of the survival time of the mouse of the test group was calculated by the following formula and obtained the survival ratio (%):

$$\text{Survival ratio (\%)} = \frac{\left[\begin{array}{l}\text{Survival time of the mouse ad-}\\\text{ministered with test compound}\end{array}\right]}{\left[\begin{array}{l}\text{Survival time of the mouse}\\\text{of the reference group}\end{array}\right]} \times 100$$

The test results are shown in Table 1 below.

Test Compound No.

1. 7-{3-[4-(3-Methylphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril
2. 7-{3-[4-(4-Methylphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril
3. 7-{3-[4-(2,3-Dimethylphenyl)-1-piperazinyl]-propoxy}carbostyril
4. 7-{3-[4-(3,4-Dimethylphenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril
5. 7-{3-[4-(3-Chloro-4-methylphenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril
6. 7-{3-[4-(3-chlorophenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril
7. 7-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propoxy}-carbostyril
8. 7-{3-[4-(4-Chlorophenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril

9. 7-{3-[4-(3-Hydroxyphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril

10. 7-{3-[4-(4-Hydroxyphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril

11. 7-{3-[4-(3-Methylphenyl)-1,2,5,6-tetrahydro-1-pyridyl]propoxy}-3,4-dihydrocarbostyril

12. 7-{3-[4-(2,3-Dimethylphenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril

13. 7-{3-[4-(Pyridyl-2-yl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril

14. 5-{3-[4-(3-Methylphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril

15. 7-{3-[4-(4-Methylphenyl)-1,2,5,6-tetrahydro-1-pyridyl]propoxy}-3,4-dihydrocarbostyril

16. 6-{3-[4-(3-Methylphenyl)-1-piperazinyl]propoxy}-2H-1,4-benzoxazin-3(4H)-one

17. 6-{3-[4-(3-Methylphenyl)-1-piperazinyl]propoxy}-2H-1,4-benzothiazin-3(4H)-one

18. 8-{3-[4-(3-Methylphenyl)-1-piperazinyl]propoxy}-2H-1,4-benzoxazin-3(4H)-one

19. 6-[3-(4-Phenyl-1-piperazinyl)propoxy]-2H-1,4-benzoxazin-3(4H)-one

20. 6-{3-[4-(2,3-Dimethylphenyl)-1-pieprazinyl]-propoxy}-2H-1,4-benzoxazin-3(4H)-one

21. 8-{3-[4-(3-Methylphenyl)-1-piperazinyl]propoxy}-2,3,4,5-tetrahydro-1H-1-benzoazepin-2-one

22. 8-{3-[4-(3-Chlorophenyl)-1-piperazinyl]-propoxy}-2,3,4,5-tetrahydro-1H-1-benzoazepin-2-one

23. 1-Methyl-7-{3-[4-(3-Chlorophneyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril

24. 7-{3-[4-(3-Methoxyphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril

25. Chloropromazine [2-Chloro-N,N-dimethyl-10H-phenothiazine-10-propamine) - Reference compound

Table 1

Test compound No.	Dosage (mg/kg, p.o.)	Survival ratio (%)
1	30	360
2	30	675
3	30	511
4	30	579
5	30	162
6	30	723
7	30	377
8	30	746
9	30	119
10	30	118
11	30	647
12	30	394
13	30	243
14	30	237
15	30	128
16	30	927
17	30	197

Table 1 (cont'd)

18	30	258
19	30	135
20	30	649
21	30	395
22	30	164
23	100	280
24	30	407
25	30	53

Example of injection preparation - 1

7-{3-[4-(4-Methylphenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril	200 mg
Glucose	250 mg
Distilled water for injection	q.s.
	5 mg

7-{3-[4-(4-Methylphenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril and glucose were dissolved in distilled water for injection, the solution was filled in an ampule of 5 ml volume. After the air in the filled ampule was replaced with nitrogen gas, the ampule was sterilized with steam under pressure at 121°C for 15 minutes to obtain the injection preparation having the above-mentioned formulation.

Example of injection preparation - 2

6-{3-[4-(3-Methylphenyl)-1-piperazinyl]-propoxy}-2H-1,4-benzoxazin-3(4H)-one	200 mg
Glucose	250 mg
Distilled water for injection	q.s.
	5 ml

By a method similar to the above-mentioned Example of injection preparation - 1, the injection preparation having the above-mentioned formulation was obtained.

Example of injection preparation - 3

8-{3-[4-(3-Methylphenyl)-1-piperazinyl]-propoxy}-2,3,4,5-tetrahydro-1H-1-benzoazepin-2-one	200 mg
Glucose	250 mg
Distilled water for injection	q.s.
	5 ml

By a method similar to that described in Example of injection preparation - 1, the injection preparation having the above-mentioned formulation was obtained.

Example of film coated tablets preparation - 1

7-{3-[4-(3-Chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril	100 g

Avicel (a trademark for microcrystalline cellulose, manufactured by Asahi Chemical Industry Co., Ltd.)	40 g
Corn starch	30 g
Magnesium stearate	2 g
TC-5 (a trademark for hydroxypropyl methylcellulose, manufactured by The Shin-Etsu Chemical Co., Ltd.)	10 g
Polyethylene glycol-6000	3 g
Castor oil	40 g
Methanol	40 g

7-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril, Avicel, corn starch and magnesium stearate were admixed together and ground, then the mixture obtained was shaped into tablets by using a tablet machine (having 10 mm in diameter). The tablets obtained were coated with a film coating consisting of TC-5, polyethylene glycol-6000, castor oil and methanol to prepare the film coated tablets having the above-mentioned formulation.

Example of film coated tablets preparation - 2

6-{3-[4-(2,3-Dimethylphenyl)-1-piperazinyl]-propoxy}-2H-1,4-benzoazin-3(4H)-one	100 g
Avicel	40 g
Corn starch	30 g
Magnesium stearate	2 g

TC-5	10 g
Polyethyle glycol-6000	3 g
Castor oil	40 g
Methanol	40 g

By a method similar to that described in Example of film coated tables preparation - 1, the film coated tablets preparation having the above-mentioned formulation were obtained.

Example of film coated tablets preparation - 3

8-{3-[4-(3-Chlorophenyl)-1-piperazinyl]-propoxy}-2,3,4,5-tetrahydro-1H-1-benzoazepin-2-one	100 g
Avicel	40 g
Corn starch	30 g
Magnesium stearate	2 g
TC-5	10 g
Polyethylene glycol-6000	3 g
Castor oil	40 g
Methanol	40 g

By a method similar to that described in Example of film coated tablets preparation - 1, there were prepared film coated tablets having the above-mentioned formulation.

Example of ointment preparation - 1

7-{3-[4-(4-Chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril	2 g
Purified lanolin	5 g
White bees wax	5 g
White petrolatum	88 g
	100 g

White bees wax was warmed to make it in a liquid state, then 7-{3-[4-(4-chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril, purified lanolin and white petrolatum were added thereto. The mixture was warmed to make it in a liquid state, then stirred until solidified to prepare the ointment having the above-mentioned formulation.

Example of ointment preparation - 2

6-{3-[4-(3-Methylphenyl)-1-piperazinyl]-propoxy}-2H-1,4-benzoazin-3(4H)-one	2 g
Purified lanoline	5 g
White bees wax	5 g
White petrolatum	88 g

By a method similar to that described in Example of ointment preparation - 1, there was prepared the ointment preparation having the above-mentioned formulation.

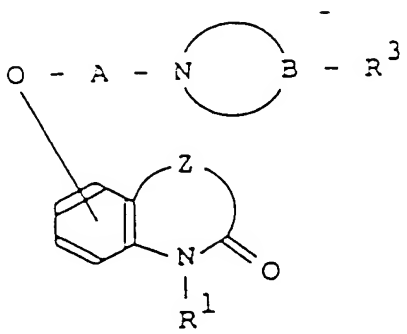
Example of ointment preparation - 3

8-{3-[4-(3-Methylphenyl)-1-piperazinyl]-propoxy}-2,3,4,5-tetrahydro-1H-benzoazepin-2-one	2 g
Purified lanoline	5 g
White bees wax	5 g
White petrolatum	88 g

By a method similar to that described in Example of ointment preparation - 1, there was prepared the ointment preparation having the above-mentioned formulation.

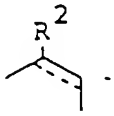
CLAIMS:-

1. A method for the preparation of a pharmaceutical composition for the treatment of hypoxia characterized in that there is used as active ingredient a compound, or salt thereof, of the formula:



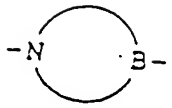
(1)

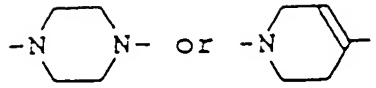
in which R^1 is a hydrogen atom or a lower alkyl, lower alkenyl, lower alkynyl or phenyl-lower alkyl group.

Z is a group of the formula  .

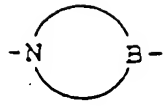
(in which R^2 is a hydrogen atom or a lower alkyl group; and the bond --- is a single or double bond), a group $-(CH_2)_3-$, $-O-CH_2-$ or $-S-CH_2-$;

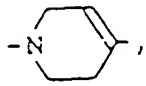
R^3 is a pyridyl group, or a phenyl group optionally substituted with up to three substituents selected from halogen atoms and lower alkyl, lower alkoxy and hydroxy groups;

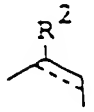
the group 

is a group 

and A is a lower alkylene group;

provided that when the group 

is a group  ,

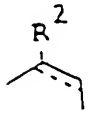
then Z is a group of the formula 

and R^3 is neither a pyridyl group nor a phenyl group having a hydroxy group as substituent; or provided that when R^3 is a pyridyl group, then Z is a group of the formula

2. A method as claimed in claim 1 in which R^3 is a phenyl group optionally substituted with up to three substituents selected from halogen atoms, C_1-C_6 alkyl groups, C_1-C_6 alkoxy groups and hydroxy groups.

3. A method as claimed in claim 2 in which R^3 is a phenyl group optionally substituted with up to two of the specified substituents.

4. A method as claimed in claim 1 in which R^3 is a pyridyl group.

5. A method as claimed in claim 3 in which Z is a group of the formula 

6. A method as claimed in claim 5 in which R^2 is a hydrogen atom.

7. A method as claimed in claim 3 in which Z is a group $-O-CH_2-$.

8. A method as claimed in claim 3 in which Z is a group $-S-CH_2-$.

9. A method as claimed in any one of claim 6, 7 or 8 in which R^1 is a hydrogen atom or a C_1-C_6 alkyl group.

10. 7-{3-[4-(4-Methylphenyl)-1-piperazinyl]propoxy}-3,4-dihydrocarbostyril;

6-{3-[4-(3-Methylphenyl)-1-piperazinyl]-propoxy}-2H-1,4-benzoxazin-3(4H)-one;

7-{3-[4-(3-Chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril;

7-{3-[4-(4-Chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyril;

7-{3-[4-(3-Methylphenyl)-1,2-5,6-tetrahydro-1-pyridyl]propxy}-3,4-dihydrocarbostyril; and

6-{3-[4-(2,3-Dimethylphenyl)-1-piperazinyl]-propoxy}-2H-1,4-benzoxazin-3(4H)-one.